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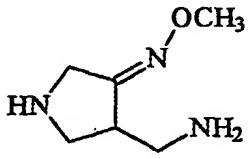
(54) Title: NOVEL PROCESS FOR PREPARING 3-AMINOMETHYL-4-Z-METHOXYIMINOPYRROLIDINE

(57) Abstract: The present invention relates to a novel process for preparing an intermediate of quinolone antibiotics Gemifloxacin, or acid addition salts thereof wherein crystallization and filtration steps of the precursor compound can be omitted, whereby the yield of the intermediate compound is drastically increased.

NOVEL PROCESS FOR PREPARING 3-AMINOMETHYL-4-Z-METHOXYIMINOPYRROLIDINE

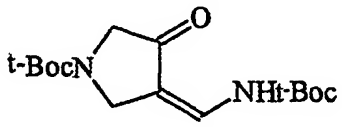
TECHNICAL FIELD

The present invention relates to a novel process for preparing a compound represented by the following formula (1):



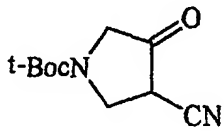
(1)

or acid addition salts thereof, an intermediate of quinolone antibiotics Gemifloxacin, via a compound represented by the following formula (3):



(3)

from a compound represented by the following formula (2):



(2)

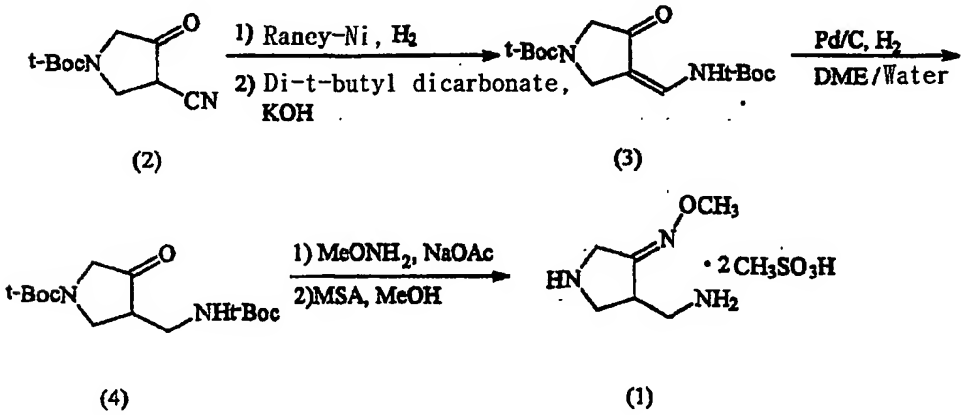
, wherein crystallization and filtration steps of the compound of formula (3) can be omitted as compared with the earlier process, whereby the yield of the desired compound of formula (1) is drastically increased.

BACKGROUND ART

The compound of formula (1) is a key intermediate for preparing the newly developed quinolone antibiotices(see Korean Patent Appln. No. 98-80504) and thus, exerts a direct influence on the manufacturing cost thereof. That is, since the yield of the compound (1) greatly affects the manufacturing cost in the commercial production, it is keenly required to design a process whereby the yield can be increased. Further, considering that the compound of formula (1) is a key intermediate of the subject material, there should be no degradation in quality due to an increase in yield.

As a process for preparing the compound of formula (1), the process as depicted in the following Reaction Scheme 1 is known. Specifically, this process comprises hydrogenating the compound of formula (2) in the presence of Raney nickel catalyst, protecting the amine group in the presence of a base, and subjecting the protected compound to crystallization and filtration to give the compound of formula (3). The compound of formula (3) is then hydrogenated under palladium catalyst to give the compound of formula (4), methyloxime group is introduced thereto, and the resulting compound is recrystallized to give the final compound of formula (1):

Reaction Scheme 1



(2) (3)

(4) (1)

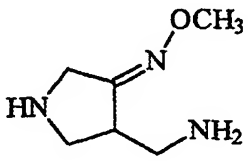
However, the above process includes crystallization and filtration in the step of preparing the compound of formula (3) during which a lot of loss in yield may occur and thus, the manufacturing cost for the compound of formula (1) may be increased.

DISCLOSURE OF INVENTION

Thus, the present inventors have conducted extensive studies to reduce the loss in yield in the step of preparing the compound of formula (3) where the degree of loss in yield is the largest in the existing process. As a result, we found that if the reaction step for preparing the compound (3) is carried out in the presence of a larger amount of base and if the hydrogenation step from the compound (3) to the compound (4) is carried out under higher temperature and hydrogen pressure than those in the existing process, the crystallization and filtration steps may be omitted as well as the deterioration of hydrogenation catalyst activity due to the use of excess base may not occur, whereby the desired compound of formula (1) can be obtained in a drastically high yield with no degradation in quality. The present invention is completed on the basis of this discovery.

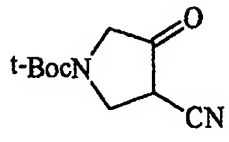
BEST MODE FOR CARRYING OUT THE INVENTION

The present invention relates to a process for preparing the compound of formula (1):



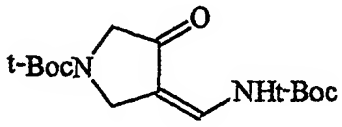
(1)

or acid addition salts thereof, which comprises hydrogenating and protecting the compound of formula (2):



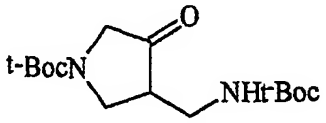
(2)

in a solvent in the presence of a catalyst and a base to give the compound of formula (3):



(3)

in Step 1, hydrogenating the resulting compound of formula (3) in a solvent in the presence of a catalyst to give the compound of formula (4):



(4).

in Step 2, and introducing methyloxime group into the resulting compound of formula (4) to give the compound of formula (1) in Step 3, wherein the base is used in an amount of 3 to 7 equivalents with respect to the compound of formula (2) and the compound of formula (3) is hydrogenated under temperatures ranging from 25 to 60℃ and hydrogen pressures ranging from 1 to 10kg/㎠.

The compound of formula (1) prepared according to the present invention may exist in such an acid addition salt form as methanesulfonate or hydrochloride.

The amount and kind of catalysts and reagents used in the present invention and the reaction conditions including the reaction temperature are as follows.

In Step 1, Raney nickel is used as the catalyst in an amount of 5 to 15% by weight with respect to the compound of formula (2).

As the base used for the purpose of controlling the concentration of hydrogen ion in the protection step of amine group, potassium- and sodium hydroxide can be mentioned. They are used in an amount of 3 to 7 equivalents with respect to the compound of formula (2).

The higher the reaction temperature is, the faster the hydrogenation reaction under Raney nickel may be completed. However, it is desirable to keep the temperature up to 40°C in order to avoid any side reactions due to the decomposition of compounds. Further, the protection reaction is carried out at temperatures of up to 10℃, preferably up to 5°C.

In Step 2, the catalyst selected from a group consisting of palladium on carbon, palladium on alumina and Raney nickel, is used in an amount of 5 to 25% by weight with respect to the compound of formula (3).

In Step 2, the hydrogen pressure varies within the range of 1 to 10kg/㎠ where the reaction temperature varies within the range of 25 to 60℃. The higher the reaction temperature, the shorter the reaction time. But, since the reactants can be decomposed at above 60℃, it is preferable to apply the temperature of up to 60℃.

All the reactions in the process according to the present invention are carried out in the same solvent. The solvent that can be used includes isopropyl alcohol, tetrahydrofuran, dimethoxyethane, etc., which are used in the form of a mixture with water in the ratio of 1 to 10 volumes with respect to 1 volume of water.

In the aspect of reaction order, the existing process comprises the steps of reacting the compound of formula (2), heating to a temperature of 40 to 60℃, separating the layers to obtain the organic layer, adding an additional solvent, cooling, crystallizing, filtering and then drying to give the compound of formula (3) as a powder. On the contrary, the process of the present invention comprises the steps of obtaining the compound of formula (3) with neither crystallization nor filtration, separating the layers to obtain the organic layer, adding catalyst, and then hydrogenating. Therefore, according to the present invention, the desired compound of formula (1) can be prepared with a high yield due to the omission of crystallization and filtration steps.

The compound of formula (1) obtained by the process according to the present invention may be used as an intermediate for preparing the quinolone antibiotics.

The present invention will be more specifically explained in the following examples. However, it should be understood that the following examples are intended to illustrate the present invention but not in any manner to limit the scope of the present invention.

EXAMPLES

Example 1

Step 1: Conversion from the compound of formula (2) to the compound of formula (3)

The compound of formula (2) (10g), Raney-nickel (1g), dimethoxyethane (57㎖) and water (10㎖) were introduced into a 300㎖ volume high pressure reactor and then stirred under 40℃ and hydrogen pressure of 4kg/㎠. After 6 hours from the reaction start, the reaction mixture was filtered through a silicious earth. To the resulting product was added 1.2 equivalent of di-t-butyl dicarbonate, which were then cooled to -10℃. The

reaction mixture was stirred for 30 minutes during which potassium hydroxide in an amount of 6 equivalents with respect to the compound of formula (2) was added thereto while maintaining the temperature of up to 5℃. After completion of reaction, 6.6 equivalents of acetic acid were added. The reaction mixture was heated to 40℃ and the organic layer was separated. The product thus obtained was analyzed by HPLC and identified that 99% of the compound of formula (2) was converted into the compound of formula (3).

Step 2: Conversion from the compound of formula (3) to methanesulfonate of the compound of formula (1)

To the organic layer prepared in the above Step 1 were added dimethoxyethane (90㎖), water (40㎖) and 5% Pd/C (1.35g). The reaction mixture was stirred for 24 hours under 50℃ and hydrogen pressure of 1kg/㎠ and then filtered to give the compound of formula (4). To the filtrate were added methoxyamine-hydrochloride (4.3g) and sodium acetate (4.2g), which was then stirred at room temperature for 4 hours. After dimethoxyethane solvent was removed, the layers were separated using ethyl acetate. Ethyl acetate in the organic layer was removed under vacuum. Then, 3 equivalents of methanol and methane-sulfonic acid were added to the residue and stirred at room temperature for 24 hours to give a product. This product was filtered and recrystallized from methanol to give 3-aminomethyl-4-Z-methoxyiminopyrrolidine dimethylsulfonate in a yield of 60% with respect to the starting compound of formula (2).

Example 2

Conversion from the compound of formula (2) to the compound of formula (3)

The same procedure as Step 1 of Example 1 was carried out except that di-t-butyl dicarbonate and potassium hydroxide were used in an amount of 1.1 equivalent and 4 equivalents, respectively. The product thus obtained was analyzed by HPLC and identified that 95% of the compound of formula (2) was converted into the compound of formula (3).

Example 3

Conversion from the compound of formula (3) to methanesulfonate of the compound of formula (1)

The same procedure as Step 2 of Example 1 was carried out using the compound of formula (3) prepared in Example 2 to give 3-aminomethyl-4-Z-methoxyimino-pyrrolidine dimethylsulfonate in a yield of 56% with respect to the starting compound of formula (2).

Comparative Example 1

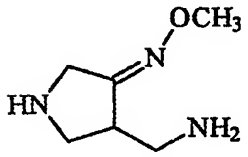
To the product obtained in Example 2 were added isopropyl alcohol (40㎖) and water (40㎖) at the same time. The resulting mixture was stirred during which water (40 ㎖) was added over two to three times. After addition, the mixture was stirred at room temperature for 12 to 16 hours, cooled to 5℃, filtered and dried. The compound thus dried was subjected to the same procedure as Step 2 of Example 1 except that dimethoxyethane was used in an amount of 15 times by volume with respect to the dried compound, borate buffer solution was added in the same amount by weight as the dried compound, and the hydrogenation reaction was carried out under room temperature and hydrogen pressure of 0.1kg/㎠. As a result, 3-aminomethyl-4-Z-methoxyiminopyrrolidine dimethylsulfonate was obtained in a yield of 43% with respect to the starting compound of formula (2).

INDUSTRIAL APPLICABILITY

According to the process of the present invention, crystallization and filtration steps of the precursor compound of formula (3) can be omitted to give the desired compound of formula (1) in a drastically high yield.

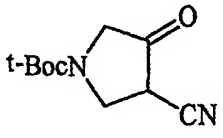
CLAIMS

1. A process for preparing a compound represented by the following formula (1):



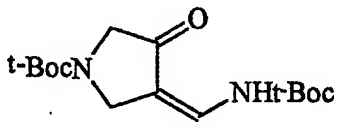
(1)

or acid addition salts thereof, which comprises hydrogenating and protecting a compound represented by the following formula (2):



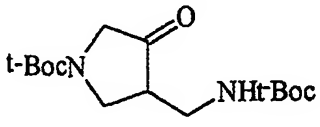
(2)

in a solvent in the presence of a catalyst and a base to give a compound represented by the following formula (3):



(3)

in Step 1, hydrogenating the resulting compound of formula (3) in a solvent in the presence of a catalyst to give a compound represented by the following formula (4):



(4)

in Step 2, and introducing methyloxime group into the resulting compound of formula (4) to give the compound of formula (1) in Step 3, wherein the base is used in an amount of 3 to 7 equivalents with respect to the compound of formula (2) and the compound of formula (3) is hydrogenated under temperatures ranging from 25 to 60℃ and hydrogen pressures ranging from 1 to 10kg/㎠.

2. The process of claim 1 wherein the protection reaction temperature in Step 1 is up to 10℃.

3. The process of claim 1 wherein the catalyst in Step 1 is used in an amount of 5 to 15% by weight with respect to the compound of formula (2) and the catalyst in Step 2 is used in an amount of 5 to 25% by weight with respect to the compound of formula (3).

4. The process of claim 1 wherein the catalyst in Step 1 is Raney nickel and the catalyst in Step 2 is selected from a group consisting of palladium on carbon, palladium on alumina and Raney nickel.

5. The process of claim 1 wherein the solvent is a mixture of an organic solvent selected from a group consisting of isopropyl alcohol, tetrahydrofuran and dimethoxyethane, and water in the ratio of 1 to 10 volumes with respect to 1 volume of water.

6. The process of claim 1 wherein the base is sodium hydroxide or potassium hydroxide.

7. The process of claim 1 wherein the compound of formula (3) is obtained with neither crystallization nor filtration in Step 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR01/01466

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 207/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimun documentation searched (classification system followed by classification symbols)

IPC : C07D 207/*

Documentation searched other than minimun documentation to the extent that such documents are included in the fileds searched

Korean Patents and application for inventions since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search trerms used)

US PTO, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,276,041호 [Kaken Pharmaceutical Co, Ltd], 04 Jan 1994 see the whole document	1 - 7
A	US 5,633,262호 [LG Chemical, Ltd], 27 May 1997 see the whole document	1 - 7
A	US 5,962,468호 [LG Chemical, Ltd], 05 Oct 1999 see the whole document	1 - 7
A	JP 89-100165호, 18 Apr 1994 see the whole document	1 - 7
A	KR 99-76521호, 15 Oct 1999 see the whole document	1 - 7

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

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"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
14 DECEMBER 2001 (14.12.2001)	17 DECEMBER 2001 (17.12.2001)

Name and mailing address of the ISA/KR	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR01/01466

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5,276,041	04 01 1994	EP 0,541,086	12 05 1993
US 5,633,262	27 05 1997	KR 96-000874	25 01 1996
US 5,962,468	05 10 1999	NONE	
JP 89-100165	18 04 1994	NONE	
KR 99-76521	15 10 1999	NONE	